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(54) 7-AMINO-2-HEPTENOATES AND THEIR USE IN THE PREPARATION OF METHYLPHENIDATE

7-AMINO-2-HEPTENOATE UND IHRE VERWENDUNG IN DER HERSTELLUNG VON METHYLPHENIDAT

7-AMINO-2-HEPTENOATES ET LEUR UTILISATION DANS LA PREPARATION DE METHYLPHENIDATE

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- **PATENT ABSTRACTS OF JAPAN vol. 002, no. 048 (C-010), 31 March 1978 & JP 53 007627 A (TEIJIN LTD), 24 January 1978, cited in the application**
- **TETRAHEDRON LETTERS, vol. 28, no. 16, 1987, OXFORD GB, pages 1757-1760, XP002031799 N. KNOUZI ET AL.: "intramolecular cyclization ....." cited in the application**

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Description

[0001] This invention relates to the synthesis of methylphenidate by cyclisation of new 7-amino-2-heptenoates.

Background of the Invention

[0002] Methylphenidate has utility as a therapeutic agent, e.g. in the treatment of attention-deficient hyperactivity disorder. It was first prepared as a mixture of the *erythro* and *threo* racemates. US-A-2957880 discloses its synthesis and also studies upon the two racemic mixtures, which revealed that the therapeutic activity resides in the *threo* diastereomer.

[0003] JP-A-53007627 discloses the formula

$$R^*\text{-NH-}(CH_2)_4\text{-CH=CH-COOR}$$

wherein R* is the chiral auxiliary α-methylbenzylamine and R is lower alkyl. This structure is indicated as suitable for cyclisation to 1-(1-phenylethyl)-2-hydroxy-5-piperidinone, en route to antihistaminic agents.

[0004] No cyclisation is demonstrated. Further, the elemental analysis of the compound that is made, consistent with the intended product, indicates that it is actually of the formula

$$R^*\text{-NH-CO-}(CH_2)_3\text{-CH=CH-COOR}$$

The fact that this is an amide may account for failure of the proposed cyclisation.

[0005] Knouzi *et al*, Tet. Lett. 28(16):1757-60 (1987), disclose cyclisation, again by Michael addition, of 7-amino-2-heptenoates of the formula

$$H_2N\text{-}(CH_2)_4\text{-CH=CR''-}COOCH_3$$

wherein R'' is H or CH_3. The resultant piperidines, and also analogous compounds, were obtained with good diastereoselectivity, except for the given compound when R'' is CH_3.

Summary of the Invention

[0006] The present invention is based on the realisation that compounds of formula I

$$Y^1Y^2N\text{-}(CH_2)_4\text{-CH=CPh-X} \qquad (I)$$

wherein Y^1 and Y^2 are independently H or a removable blocking group, or Y^1 and Y^2 together are a removable divalent blocking group, and X is $COOCH_3$ or a group convertible thereto, are novel intermediates that provide the basis of a new synthesis of methylphenidate. Further, cyclisation by Michael addition proceeds substantially only on one of the two geometric isomers. Thus, contrary to the most closely analogous situation in the prior art, effective and useful diastereoselectivity is found.

[0007] Therefore, according to a further aspect of this invention, compounds of formula I when Y^2 is H can be converted to methylphenidate by Michael addition, using a base such as lithium diethylamine, removing any blocking group represented by Y^1, and converting X to $COOCH_3$, if necessary.

[0008] According to yet another aspect of the invention, compounds of formula I may be prepared by a Horner-Wadsworth-Emmons reaction of corresponding compounds of the formulae Ph-CHX-PO(Oalk)$_2$ and $Y^1Y^2N\text{-}(CH_2)_4\text{-CHO}$, wherein Y^2 is a blocking group; and, if desired, removing the blocking group to give the product in which Y^2 is H.

Description of the Invention

[0009] X is preferably $COOCH_3$. Alternatively, it may be CN, $CONH_2$ or $COOR^1$, R^1 being H or alkyl or aralkyl of up to 10 C atoms. Other groups X that can readily be converted to $COOCH_3$, and methods of conversion, will be readily apparent to one of ordinary skill in the art.

[0010] Y^1 and Y^2 may each be H. Either or each, or the two together, may also be a blocking group. Groups that can readily be introduced onto a N atom, and readily removed after another part of the molecule has undergone reaction, are well known to those of ordinary skill in the art. For example, reference may be made to T.W. Greene *et al*, "Protecting Groups in Organic Synthesis", 2nd ed. Wiley-Interscience, New York (1991). A particular example of a suitable blocking group is t-butyloxycarbonyl (Boc). An example of Y^1 and Y^2 together with N is phthalimido.

[0011] In certain circumstances, it may be preferred that Y^1 is a chiral auxiliary, in single enantiomer form. A preferred example is 1-phenylethyl, which may be introduced using, say, α-methylbenzylamine (α-MBA), and removed by hydrogenation. The use of a chiral auxiliary may assist control of absolute and/or relative stereochemistry. Either enantiomer may be used, depending on the desired product, and this may readily be determined by experiment. Any *erythro* diastereoisomer formed by cyclisation may be subjected to epimerisation at the benzylic position to give optically-enriched *threo* methylphenidate or a derivative thereof.

[0012] Each of the reactions described herein may be conducted by generally known methodology, and any variations that may be necessary for optimisation can readily be determined by one of ordinary skill in the art. Any desired resolution, e.g. to obtain *d-threo*-methylphenidate, may be conducted by known means. Preferred resolution processes are described in PCT/GB97/00185 and PCT/GB97/00643. Such resolutions may be combined with the racemisation described in PCT/GB97/00281. The contents of these copending Applications are incorporated herein by reference.

[0013] Scheme 1 illustrates a synthesis of a racemic compound of formula I. Scheme 2 illustrates a synthesis of optically pure compound of formula I, starting from glutaric anhydride and optically-pure α-MBA. The four steps of Scheme 1 are further illustrated by the following Examples 1 to 4, respectively. Example 5 illustrates the cyclisation by Michael addition.

Example 1

[0014] 5-Amino-1-pentanol (30.0 g, 0.29 mol) and acetophenone (34.9 g, 0.29 mol) were condensed by refluxing in toluene (100 ml) under Dean and Stark conditions in the presence of 1% $ZnCl_2$ (20 mg). Toluene was removed and substituted with MeOH (100 ml), and then $NaBH_4$ (10.8 g, 0.29 mol) was added to reduce the imine. MeOH was removed and the product was partitioned between EtOAc (150 ml) and water (150 ml). After aqueous workup, the amine was obtained as a yellow oil (51 g, 85%).

Example 2

[0015] The secondary amine was protected by a Boc group. The amine (38.0 g, 18 mol) was treated with 1 eq Boc_2O (39.9 g, 0.18 mol) in a biphasic mixture of THF/2M NaOH (200 ml) for 2 hrs. The product was chromatographed on silica using EtOAc/heptane 1:1 to afford the Boc-protected amide (50.0 g, 89%).

Example 3

[0016] The alcohol (17.0 g, 0.55 mol) was oxidised to the aldehyde using standard conditions (DMSO-oxalyl chloride-TEA) (3:1.5:7 in DCM). The crude product was chromatographed through silica with EtOAc/heptane 2:8, to afford the aldehyde as a yellow oil (11.52 g, 68%).

Example 4

[0017] Methyl (+)-2-bromophenylacetate (51.14 g, 96%) was prepared from the free acid (50.0 g, 0.23 mol) in 96% yield with 1 eq of acetyl chloride (18.3 g, 16.5 ml) in methanol (20 ml) at room temperature. Triethyl phosphite (12.35 ml, 0.72 mol) was added over a period of 20 minutes to methyl α-bromophenyl acetate (15.0 g, 0.65 mol) at 120°C, and then the mixture was heated for 3 hrs at 160°C. The phosphonate was isolated cleanly in quantitative yield (19.5 g, 100%).

[0018] 1 M $(Me_3Si)NNa$ (4.9 ml) was added to a solution of the phosphonate (1.4 g, 4.91 mmol) in THF (5 ml) at -78°C. A solution of the aldehyde (1.0 g, 3.27 mmol) in THF (5 ml) was added dropwise. The solution was warmed to room temperature overnight. After aqueous workup, a 1:1 mixture of the geometric isomers of formula I was obtained (0.89 g; 66%).

[0019] Treatment of the Boc-protected amino-alkene (0.89 g, 2.0 mmol) with neat TFA (2 ml) cleanly removed the Boc group. The trifluoroacetate salt was treated with TEA (2 ml) in MTBE (5 ml). Surprisingly, the free amine was isolated rather than the cyclised product (0.69 g; 101%).

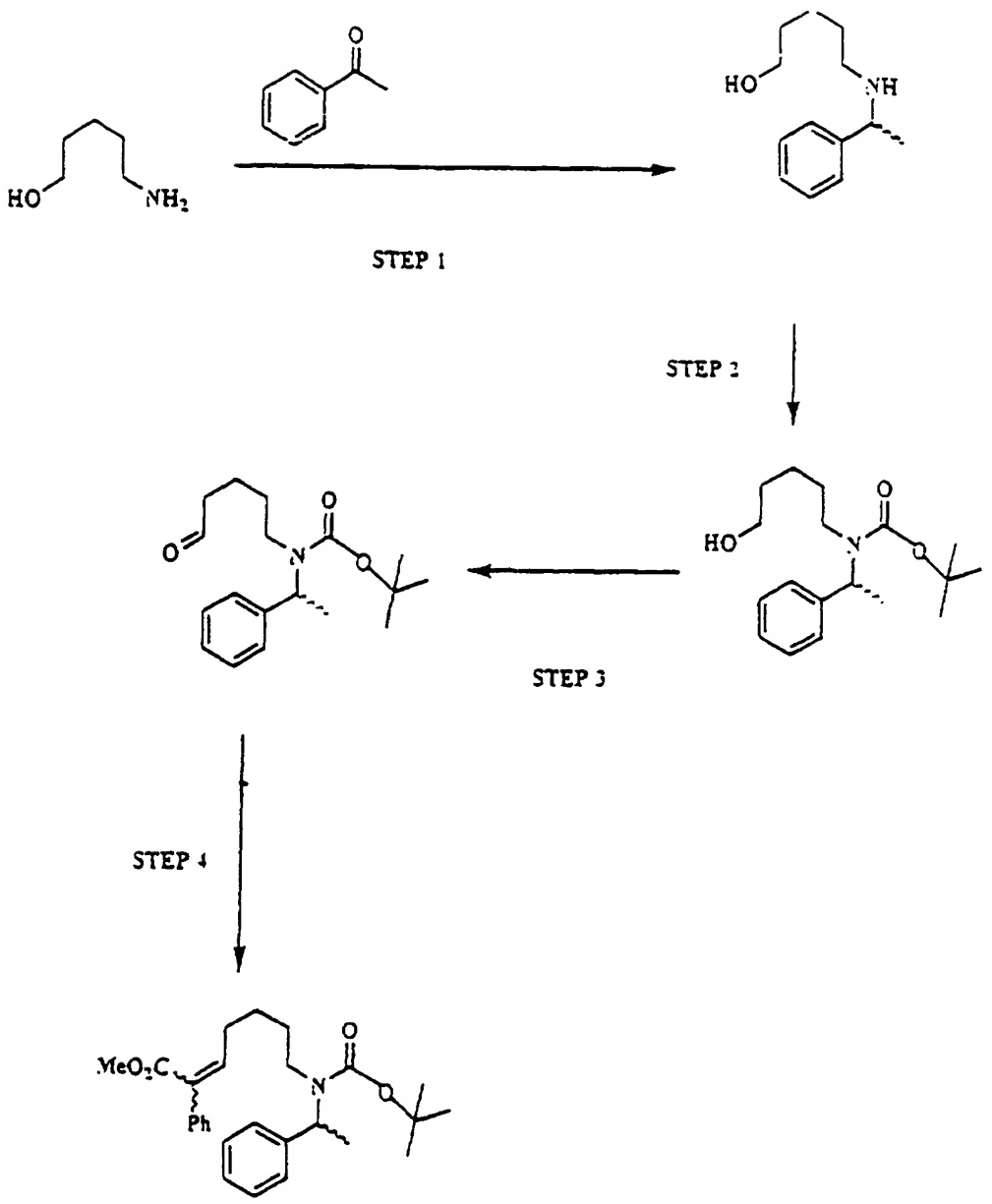
Example 5

[0020] A dilute solution of the free amine (0.66 g, 1.98 mmol) in THF (10 ml) was added dropwise to freshly prepared 0.28 MLDA (8.5 ml, 2.38 mmol) in THF (50 ml) at -78°C. The mixture was then warmed to -20°C over 2 h, before being quenched with saturated ammonium chloride.

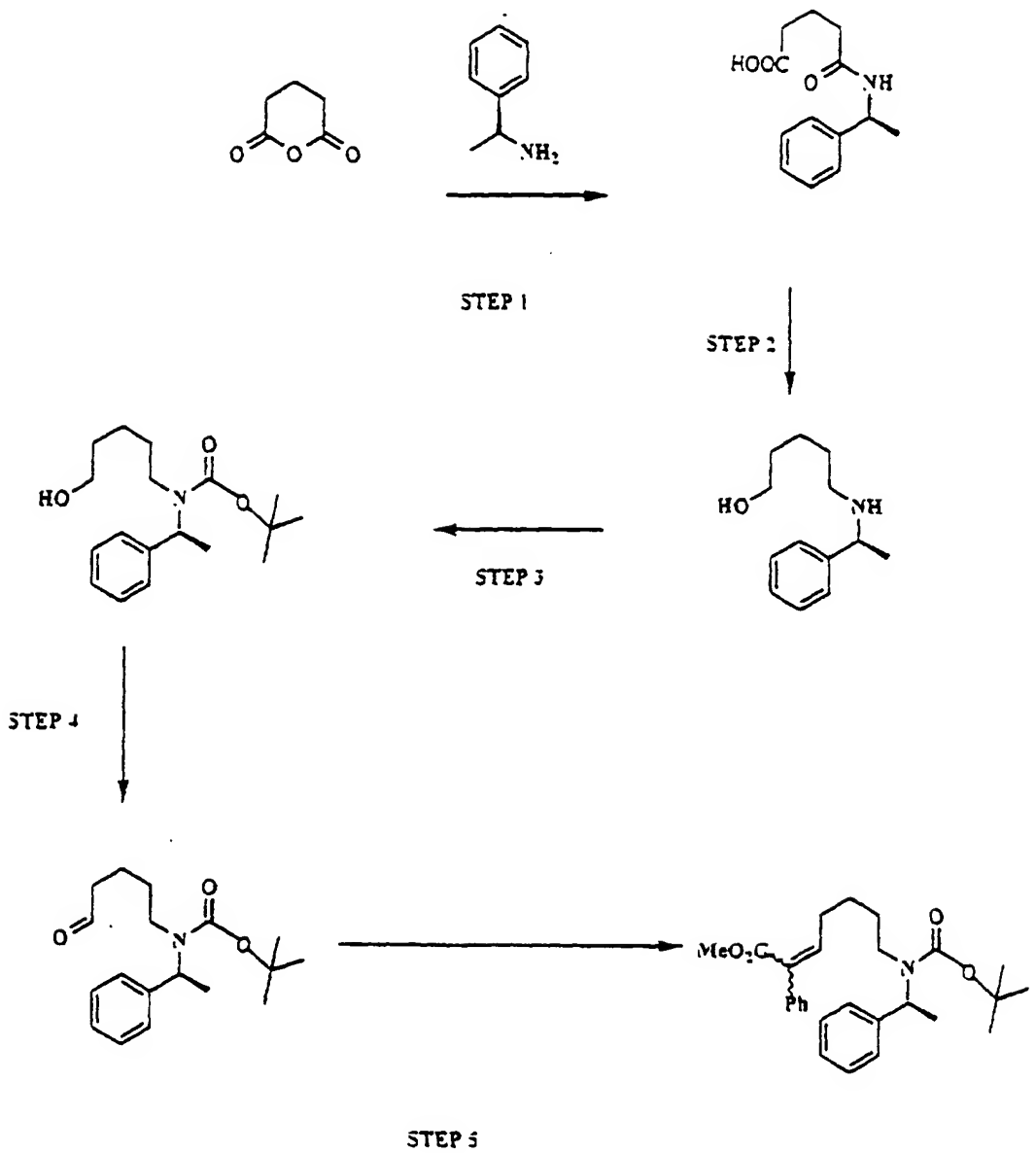
[0021] The ^{1}H NMR spectrum of the crude product showed that one geometric isomer of the starting material had not reacted while the other isomer had undergone a Michael addition. Column chromatography of the product mixture gave a single geometric isomer of unreacted amine and the cyclised product.

[0022] The sample of cyclised material is not completely pure, but the 'H NMR spectrum indicates that 2:1 mixture of major diastereomers has been produced. In theory, four diastereomers could be produced in this reaction, therefore there is good diastereoselectivity.

Scheme 1



Scheme 2



Claims

1. A compound of the formula

$$Y^1Y^2N\text{-}(CH_2)_4\text{-}CH{=}C(Ph)\text{-}X$$

wherein Y^1 and Y^2 are independently H or a removable blocking group, or Y^1 and Y^2 together are a removable

divalent blocking group; and X is $COOCH_3$ or a group convertible thereto.

2. A compound according to claim 1, wherein X is CN, $CONH_2$ or $COOR^1$, R^1 being H or alkyl or aralkyl of up to 10 C atoms.

3. A compound according to claim 1 or claim 2, wherein Y^1 is H or a chiral auxiliary.

4. A compound according to any preceding claim, wherein Y^1 is 1-phenylethyl.

5. A compound according to claim 3 or claim 4, wherein Y^2 is H.

6. A process for preparing a compound according to any preceding claim, which comprises a Horner-Wadsworth-Emmons reaction of corresponding compounds of the formulae Ph-CHX-$PO(Oalk)_2$ and Y^1Y^2N-$(CH_2)_4$-CHO, wherein Y^2 is a blocking group; and, if desired, removing the blocking group to give the product in which Y^2 is H.

7. A process for preparing methylphenidate, which comprises a Michael reaction, using base, on a compound according to claim 5; removing any blocking group represented by Y^1; and, if X is not $COOCH_3$, converting it to $COOCH_3$.

8. A process according to claim 7, wherein the base is lithium diethylamine.

9. A process according to claim 7 or claim 8, wherein Y^1 is 1-phenylethyl and it is removed by hydrogenation.

Patentansprüche

1. Verbindung der Formel

$$Y^1Y^2N\text{-}(CH_2)_4\text{-}CH{=}C(Ph)\text{-}X$$

worin Y^1 und Y^2 unabhängig für H oder eine entfernbare blockierende Gruppe stehen oder Y^1 und Y^2 zusammen für eine entfernbare zweiwertige blockierende Gruppe stehen; und X für $COOCH_3$ oder eine Gruppe, die dazu umgewandelt werden kann, steht.

2. Verbindung nach Anspruch 1, worin X für CN, $CONH_2$ oder $COOR^1$ steht, worin R^1 für H oder Alkyl oder Aralkyl mit bis zu 10 C-Atomen steht.

3. Verbindung nach Anspruch 1 oder Anspruch 2, worin Y^1 für H oder einen chiralen Hilfsstoff steht.

4. Verbindung nach einem der vorstehenden Ansprüche, worin Y^1 für 1-Phenylethyl steht.

5. Verbindung nach Anspruch 3 oder Anspruch 4, worin Y^2 für H steht.

6. Verfahren zur Herstellung einer Verbindung nach einem der vorstehenden Ansprüche, das eine Horner-Wadsworth-Emmons-Reaktion der entsprechenden Verbindungen der Formeln Ph-CHX-$PO(Oalk)_2$ und Y^1Y^2N-$(CH_2)_4$-CHO, worin Y^2 für eine blockierende Gruppe steht; und gegebenenfalls die Entfernung der blokkierenden Gruppe, um das Produkt, in dem Y^2 für H steht, zu erhalten, umfasst.

7. Verfahren zur Herstellung von Methylphenidat, das eine Michael-Reaktion unter Verwendung einer Base mit einer Verbindung nach Anspruch 5; die Entfernung jeglicher blockierender Gruppen, die durch Y^1 dargestellt werden; und, falls X nicht für $COOCH_3$ steht, dessen Umwandlung in $COOCH_3$, umfasst.

8. Verfahren nach Anspruch 7, worin es sich bei der Base um Lithiumdiethylamin handelt.

9. Verfahren nach Anspruch 7 oder Anspruch 8, worin Y^1 für 1-Phenylethyl steht und durch Hydrierung entfernt wird.

Revendications

1. Composé de formule

$$Y^1Y^2N\text{-}(CH_2)_4\text{-}CH{=}CPh\text{-}X \qquad (I)$$

où Y^1 et Y^2 sont, de façon indépendante, H ou un groupe bloquant pouvant être éliminé, ou bien Y^1 et Y^2 forment, ensemble, un groupe bloquant divalent pouvant être éliminé, et X est $COOCH_3$ ou un groupe pouvant être converti en ce reste.

2. Composé selon la revendication 1, dans lequel X est CN, $CONH_2$ ou $COOR^1$, R^1 étant H ou un alkyle ou un aralkyle ayant jusqu'à 10 atomes de carbone.

3. Composé selon la revendication 1 ou la revendication 2, dans lequel Y^1 est H ou un auxiliaire chiral.

4. Composé selon l'une quelconque des revendications précédentes, dans lequel Y^1 est le 1-phényléthyle.

5. Composé selon la revendication 3 ou la revendication 4, dans lequel Y^2 est H.

6. Procédé pour la préparation d'un composé selon l'une quelconque des revendications précédentes, qui comprend une réaction de Horner-Wadsworth-Emmons des composés correspondants de formule $Ph\text{-}CHX\text{-}PO(Oalk)_2$ et $Y^1Y^2N\text{-}(CH_2)_4\text{-}CHO$, où Y^2 est un groupe bloquant ; et si on le désire, l'élimination du groupe bloquant pour obtenir le produit dans lequel Y^2 est H.

7. Procédé pour la préparation du méthylphénidate, qui comprend une réaction de Michael, en utilisant une base, sur un composé selon la revendication 5 ; l'élimination, le cas échéant, du groupe bloquant représenté par Y^1 ; et, si X n'est pas $COOCH_3$, sa conversion en $COOCH_3$.

8. Procédé selon la revendication 7, dans lequel la base est le diéthylamidure de lithium.

9. Procédé selon la revendication 7 ou la revendication 8, dans lequel Y^1 est 1-phényléthyle et est éliminé par hydrogénation.